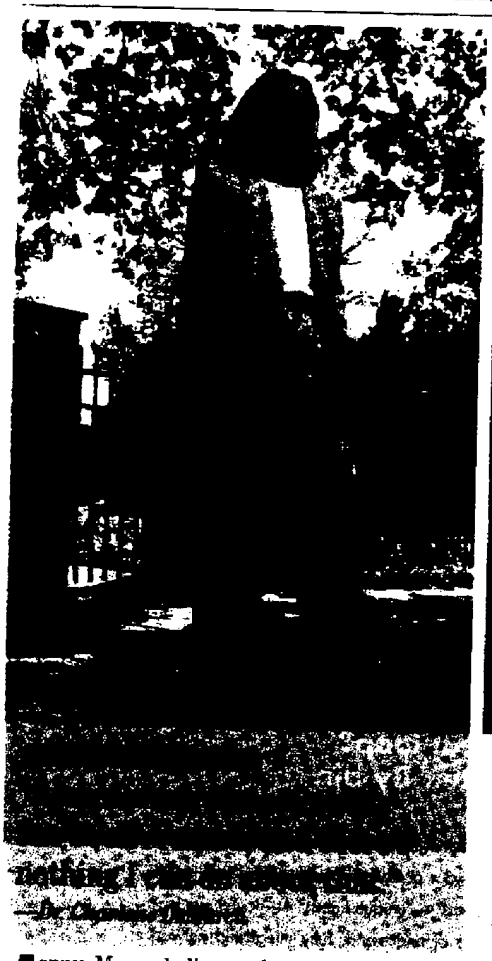
MEDICINE

A VACCINE WORSE THAN THE DISEASE?

Angry patients claim that LYMErix presents serious risks



SAFE FOR CHILDREN

"I would never have participated in pediatric studies if I believed it was harmful."

—Dr. Neil Halsey

Jenny Marra believes that LYMErix, the Lyme disease vaccine available since 1998, seriously harmed her. 42-year-old nurse from Ocean Town-, N.J., has suffered crippling joint muscle pain, fatigue, and periods aralysis since receiving a second of the vaccine in June, 1999. Other pain management, Marra's doctors her there is nothing more they can n April, she filed a lawsuit against vaccine's maker, SmithKline ham Corp., seeking unspecified ages. Her goal: "I'm trying to stop [the Food & Drug Administration] from approving the vaccine for children."

Dr. Neil A. Halsey feels exactly opposite. As director of the Institute for Vaccine Safety at Johns Hopkins University's School of Public Health, Halsey was an investigator in the pediatric trials of LYMErix, now approved only for use in adults. The results of the trial, which included 5,000 children aged 4 to 18, showed that LYMErix is safe and even more effective in kids than it is in adults, he says. The FDA is reviewing the study and other data as part of SmithKline's application to market LYMErix for children. "I would never have participated in pediatric studies if I believed it was harmful," says Halsey.

Halsey has some big guns on his side. The Centers for Disease Control & Prevention and the FDA also support the vaccine's use in adults at risk of contracting Lyme disease. SmithKline has distributed 1.3 million doses of the vaccine to an estimated 600,000 people.

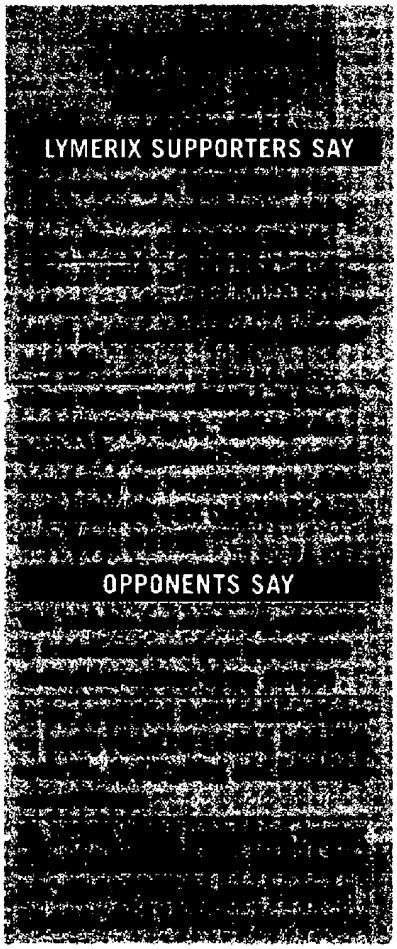
FACIAL PARALYSIS. Nevertheless, there is a growing and vocal group of doctors, lawyers, and patients—including Marra—who are staunchly opposed. They believe that up to 30% of the population may carry a gene that raises the risk for debilitating autoimmune problems after receiving the vaccine. They point to reports of some 761 adverse reactions—including arthritis and facial paralysis—recorded by the government's Vaccine Adverse Event Reporting System (VAERS) in the two years that LYMErix has been on the market. Individuals have filed lawsuits in three states against SmithKline Beecham. And the Philadelphia law firm Sheller, Ludwig, & Badey has filed a class action against the company on behalf of people who have been vaccinated and now require further expensive tests. "The vaccine should be withdrawn from the market," says Dr. Ronald F. Schell, a Lyme disease researcher at the University of Wisconsin, who published a study showing that the vaccine can induce arthritis in hamsters. "I don't think it's safe for anyone."

LYMErix has always been controversial. Initial concerns arose over how much protection it would actually afford. Lyme disease is transmitted to humans via the common deer tick. Some of these ticks harbor in their gut a bacterium called *Borrelia burgdorferi*. After they bite their human hosts, they transfer the bug into the bloodstream.

When developing a vaccine, researchers focused on a protein found on the outer surface of *B. burgdorferi* called OspA. The theory is that when a person receives an injection of a recombinant version of this protein, the body

makes antibodies against OspA. If an infected tick then bites the vaccinated individual, the antibodies will neutralize any bacteria before they cause disease.

In the mid-1990s, Dr. Thomas G. Schwann and other researchers at the Rocky Mountain Laboratory in Hamilton, Mont., part of the National Institutes of Health, confirmed that *B. burgdorferi* displayed OspA on its outer membrane while in the tick's gut. But they also found that once the bacteria moved into humans, it replaced the protein with another, called OspB. In people who have been vaccinated against Lyme, most bacteria in the tick's gut are killed because the tick sucks in blood carrying neutralizing antibodies. But some bacteria may slip by, evade detection, and cause disease. This may explain why the Lyme vaccine is only 78% effective, even after three doses. "Vaccinating with OspA could give people the illusion that they are protected," says Schell.



As far back as 1995 there were also concerns about possible side effects from the shot. Dr. Alan Steere, a Lyme researcher at New England Medical Center in Boston, noted in a letter to the FDA that some early trial participants complained of joint and muscle pain. Then, in July, 1998—six months before LYMERix was approved—Steere published a paper in the journal *Science* that sought to explain the cause of debilitating arthritis in a small minority of long-term Lyme disease sufferers. Steere researchers found that OspA can potentially cross-react with a human protein in individuals who carry a gene called HLA-DR4. When that happens, the body's immune system could mistakenly attack human proteins, thinking they are Lyme bacteria.

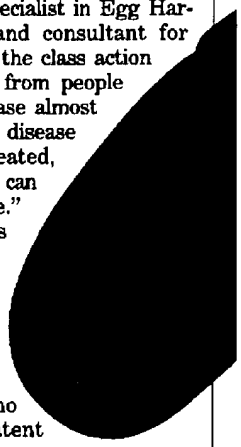
Steere's study involved antibodies removed from the joints of people who had Lyme disease-associated arthritis, not from people who had received the vaccine. Still, SmithKline was aware of the theoretical possibility that there could be autoimmune problems with their vaccine. In all, 10,000 adults enrolled in two different trials received recombinant OspA vaccines. Half were part of the LYMERix study and an additional 5,000 took part in a trial of a competing vaccine then being developed by Connaught Laboratories Inc.—now a part of Aventis Pasteur Inc. in Swiftwater, Pa. Connaught has since shelved its OspA vaccine, deciding instead to work on a "second-generation" vaccine that contains three antigens instead of just one.

The vaccine studies, published in the *New England Journal of Medicine*, found no evidence of increased incidence of autoimmune problems such as arthritis or any other serious side effects. In continued monitoring of the vaccine after approval, "we are seeing no unusual patterns coming through," says Carmel Hogan, a spokeswoman for SmithKline. Officials at the FDA and the CDC support these findings.

SmithKline says that its investigators went a step further in tracking down any autoimmune problems. They conducted a second, unpublished study of 300 vaccine recipients with the HLA-DR4 gene. No ill effects were seen during a two-year period. But Tom Forschner, executive director of the Lyme Disease Foundation Inc. in Hartford, Conn., complains that he has been asking to see this study for nine months, to no avail. He wonders why the company, in the face of a lawsuit, would not make the data public. The company says it is in the process of getting this study and others published.

For now, controversy is only increasing. Some lawyers involved in the class action have charged that vaccine researchers receive funding from SmithKline and therefore can't be impartial. Halsey, for one, did get funding from SmithKline to conduct his pediatric study, but says he has no financial stake in the company. "I can't make any money from my recommendation," he notes.

Meanwhile, Dr. Charlene DeMarco, an emerging disease specialist in Egg Harbor, New Jersey, and consultant for lawyers involved in the class action says she gets calls from people harmed by the disease almost daily: "A whole new disease entity has been created, and there's nothing I can do for these people." Forschner says his foundation has also been receiving calls about people who have allegedly suffered bad reactions to the vaccine—including people who claim that their latent Lyme infections were revived by vaccination.



DEER TICK

So far, there has been no peer-reviewed research on adverse reactions. Taken against the backdrop of an estimated 600,000 people who have received the vaccine, the cases don't raise red flags at the FDA or the CDC. "Just because [arthritis] happens to some people and a bunch of lawyers say it's caused by the Lyme vaccine doesn't make it true," says Dr. Eugene Shapiro, a professor at Yale University School of Medicine.

SALES HIT. Still, anecdotal evidence of adverse reactions may have affected sales. Some doctors have been reluctant to give patients the shots or are ordering $300 HLA-DR4 tests before they vaccinate. SmithKline's sales of the vaccine have dropped from $21.5 million last year to $17.6 million this year, according to IMS Health Inc., a health-care-information company. Pediatric approval would increase the market for LYMERix, but it would also increase the company's exposure to liability.

Ultimately, it looks as if LYMERix is not the panacea some were optimistically expecting. Lyme disease is still not fully understood, and questions remain about its connection to autoimmune disease. The best approach may be to let independent researchers review all available vaccine data—including unpublished studies. Until then, the vaccine's fate may be decided in the courts of law and public opinion.

By Naomi Freundlich in New York